REMARKS

Claims 1-19 are pending. Claims 13-19 are withdrawn from consideration. Claims 1-12 are rejected. Reconsideration is requested.

Amendment to the claim language has been made solely to overcome indefiniteness rejections and to put the claims into acceptable U.S. form. No new matter has been added. The change from "fetal T lymphocytes" to "immature T lymphocytes" is supported at page 8, lines 3 to 11, wherein the definition of "fetal T lymphocytes" is provided as follows: "Fetal T lymphocytes of the present invention means T lymphocytes before they develop to mature T lymphocytes". Though the meaning of "immature" was translated into the term "fetal" in translation from Japanese into English, the term "fetal" has a meaning related to "fetus; foetal: (unborn child)", and therefore the term "fetal T lymphocytes" has been changed to "immature T lymphocytes" in order to avoid confusion.

The Examiner indicated that the Information Disclosure Statement did not satisfy PTO requirements because it failed to provide the titles of the Journals for citations AG-AI, AK and AM. A revised PTO/SB/08A is submitted herewith. It is not believed that any fee is due, as the references listed were submitted with the original IDS. However, please charge any additional necessary fee to our deposit account, as noted on the first page of this Amendment, and notify the undersigned.

1. Rejection of claims 1, 3-8, and 10-12 under 35 USC §102

Claims 1-12 were rejected under 35 USC § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims have been amended to remove the term "characterized", and to recite active method steps as appropriate. In addition, the term "mediated" has been removed. Claims 8 and 9 have been amended and are believed to be free of the rejection. Reconsideration is respectfully requested.

2. Rejection of claims 1, 3-8, and 10-12 under 35 USC §102

Claims 1, 3-8, and 10-12 were rejected under 35 U.S.C. 102 (b) as being anticipated by DeMatteo et al. (1997) J. Virol., Vol. 71 (7), 5330-5335.

It is the Examiner's position that DeMatteo et al. teaches "the direct injection of a recombinant adenovirus encoding a gene of interest into thymus at a time before T-cell maturation had occurred resulting in the induction of tolerance to the adenoviral proteins, and encoded foreign gene product." However, with regard to the administration method, as shown by DeMatteo et al., the virus was administered intravenously and directly to thymus (DeMatteo et al., page 5330, abstract).

In contrast, as shown in the amended claims, the present invention comprises a method of acquiring immunological tolerance to a foreign DNA and/or its expression product comprising: providing an immature T lymphocyte transferred with the foreign DNA; introducing the immature T lymphocyte into thymus. In other words, unlike DeMatteo et al. wherein a foreign DNA is directly introduced into thymus, the present invention comprises effective acquirement of immunological tolerance by transferring said foreign DNA into immature T lymphocytes and introducing said immature T lymphocytes into thymus. The present invention was the first to disclose this method.

The method wherein adenoviral vector is directly injected into thymus, as in DeMatteo et al., is an impractical method with a high risk because a pharmaceutical is administered systemically and it is probable that there arise problems caused by systemic administration such as toxicity of adenovirus or leakage at the time of administration. In fact, it is reported that systemic administration of adenoviral vector might result in death (Raper, Human Gene Therapy 13, 163, 2002; St George, Gene Therapy 10, 1135, 2003). On the other hand, the present inventors have succeeded in effective acquirement of immunological tolerance by introducing only immature T lymphocytes transferred with a foreign DNA, wherein a gene expressed for gene therapy is incorporated into a vector such as adenovirus, into thymus. As only "immature T lymphocytes transferred with a foreign DNA" are administered into thymus, it is possible to provide a realistic

method that is much safer, without a probability of problems such as toxicity of adenovirus or leakage at the time of administration caused by systemic administration of pharmaceuticals as in DeMatteo et al.

As described above, the claimed invention is, as it is apparent from the pending claims, different from the invention mentioned in DeMatteo et al. Accordingly, it is respectfully requested that the 35 U.S.C. 102 (b) rejection be withdrawn.

3. Rejection of claims 1-12 under 35 USC §103

Claims 1-12 were rejected under 35 U.S.C. 103 (a) as being unpatentable over Ilan et al. (1996), in view of DeMatteo et al. (1997), and further in view of Bakker et al. (1999).

The difference between the present invention and DeMatteo et al. is detailed in the above paragraphs. As apparent from the description in the above paragraphs, we respectfully submit that the present invention is not anticipated by DeMatteo et al. and is not obvious.

Ilan et al, which is cited by the Examiner, indicates "central tolerance induction to adenoviral antigens by directly injecting a recombinant adenovirus encoding a therapeutic gene" (Ilan et al., page 2640, abstract), as pointed out by the Examiner. However, there is neither description nor suggestion as to effective acquirement of immunological tolerance by transferring a foreign DNA into immature T lymphocytes and introducing said immature T lymphocytes into thymus.

In contrast, as recited in the pending claims, the present invention comprises a method of acquiring immunological tolerance to a foreign DNA and/or its expression product comprising: providing an immature T lymphocyte transferred with the foreign DNA; introducing the immature T lymphocyte into thymus. In other words, unlike Ilan et al. wherein a foreign DNA is directly introduced into thymus, the present invention comprises effective acquirement of immunological tolerance by transferring said foreign DNA into immature T lymphocytes and introducing said

immature T lymphocytes into thymus. The present invention was the first to disclose this method.

Further, as stated above with regard to the case of DeMatteo, the method wherein adenoviral vector is directly injected into thymus, as in Ilan et al., is an impractical method with a high risk because a pharmaceutical is administered systemically and it is probable that problems will arise caused by systemic administration such as toxicity of adenovirus or leakage at the time of administration. In fact, it is reported that systemic administration of adenoviral vector might result in death (Raper, Human Gene Therapy 13, 163, 2002; St George, Gene Therapy 10, 1135, 2003). In contrast, the present inventors have succeeded in effective acquirement of immunological tolerance by introducing only immature T lymphocytes transferred with a foreign DNA, wherein a gene expressed for gene therapy is incorporated into a vector such as adenovirus, into thymus. As only "immature T lymphocytes into which a foreign DNA is transferred" are administered into thymus, it is possible to provide a realistic method wherein much more safety is secured, without a probability of problems such as toxicity of adenovirus or leakage at the time of administration caused by systemic administration of pharmaceuticals as in Ilan et al.

As noted above, the claimed invention described is completely different from the invention mentioned in Ilan et al. and is not taught by Ilan et al., as in the case of DeMatteo et al. Therefore, it is respectfully submitted that the claimed invention is not obvious from the combination of DeMatteo et al. and Ilan et al."

In Bakker et al., which is cited by the Examiner, there is a description of "fetal thymocytes infected with adenovirus containing mut-IkB."

However, Bakker et al. does not teach the present invention because there is no description regarding immunological tolerance for adenoviral vector in Bakker et al.

As stated above, even when the descriptions of Bakker et al., DeMatteo et al. and Ilan et al. are considered together, the present invention is not taught by those descriptions. Therefore, it is respectfully requested that the rejection of claims 1-12 as being unpatentable over Ilan et al. (1996),

in view of DeMatteo et al. (1997), and further in view of Bakker et al. (1999)" be withdrawn.

All rejections having been addressed, it is respectfully submitted that the application is in order for allowance, and Notice to that effect is respectfully requested.

Respectfully submitted,

Date: 7/14/04

Ann S. Hobbs, Ph.D.
Registration No. 36,830
VENABLE
P.O. Box 34385
Washington, D.C. 20043-9998
Telephone: (202) 344-4000